82. (new) The method of Claim 80 wherein the plasminogen activator is selected from the group consisting of urokinase, streptokinase and tissue plasminogen activator.

83. (new) The method of Claim 80 further comprising administering plasminogen.

84. (new) The method of Claim 80 further comprising administering plasmin.

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85. (new) The method of Claim 80 wherein said animal is a human.

86. (new) The method of Claim 80 wherein said angiogenic disease is a neoplastic disease.

87. (new) The method of Claim 86 wherein the neoplastic disease is a malignant tumor.

88. (new) The method of Claim 86 wherein the neoplastic disease is a benign tumor.

## REMARKS

Claims 19-21 and 24 have been amended. Claims 76-88 have been added. The amendments and new claims are fully supported by the specification and do not constitute new subject matter as defined in 35 U.S.C. § 132. Specifically, amended Claims 19-21, 24, and new Claims 76-88 are supported by the specification at page 3, line 12 to page 4, line 7 and page 18, line 26 to page 20, line 10 (describing a method of treating an animal suffering from an angiogenic disease by administering a plasminogen activator alone or in combination with a sulfhydryl donor, plasminogen, and/or plasmin in an amount to produce a therapeutic effect); page 10, lines 1-7, 14-18 (describing specific plasminogen activators and sulfhydryl donors); page 48, line 4 to page 51, Table 4 and Figures 17A and 17B (detailing

the treatment of several human cancer patients by administering plasminogen activator alone or in combination with a sulfhydryl donor).

Claims 19-21, 23, 24, and 76-88 will be pending upon entry of the instant amendment. A marked-up version of the claims amended herein indicating the deletion and addition of matter by bracketing and underlining, respectively, is attached hereto as Exhibit A. A copy of the claims that will be pending upon entry of the instant amendment is attached hereto as Exhibit B.

The Applicant respectfully requests that the amendments made herein be entered into the file of the above-identified application and that the remarks be fully considered.

## 1. Election/Restriction and Priority Date

The Applicant wishes to thank the Examiner for combining Groups XXI and XXII and believes that the amendments made herein and new claims would be classified under previously elected Group V.

The Examiner states that parent U.S. Application Nos. 08/991,761 and 08/710,305 to which priority is claimed does not describe "a method of treating an angiogenic disease, comprising administering a plasminogen activator and optionally a sulfhydryl donor." The Applicant respectfully submits that the amended claims and new claims are in fact fully supported by parent U.S. Application Nos. 08/991,761 and 08/710,305.

With respect to U.S. Application No. 08/991,761, the Applicant invites the Examiner's attention to page 3, line 24 to page 4, line 13 (describing a container holding a plasminogen activator alone or in combination with a sulfhydryl donor with instructions for administering the plasminogen activator alone or in combination with a sulfhydryl donor to an animal suffering from an angiogenic or neoplastic disease); page 10, line 31 to page 11, line 6 (disclosing specific plasminogen activators); page 11, lines 16-23 (disclosing specific sulfhydryl donors); page 21, line 16 to page 22, line 29 (disclosing the treatment of specific angiogenic diseases and a dose of plasminogen activator alone or in combination with a sulfhydryl donor effective to produce a "therapeutic effect"); page 23, lines 17-18 (disclosing that it is "possible" for any "compound of the present invention to be administered alone," such as plasminogen activator with or without a pharmaceutical formulation); page 24, lines

7-12 (describing therapeutically effective doses of the active ingredient); page 50, lines 7-25 including Figures 7-9, & 12 (teaching that an amount of angiostatin may be generated by plasminogen activators administered in the presence of "flow-through" containing sulfhydryl donors thereby indicating that the *in vivo* administration of plasminogen activator alone may generate angiostatin in the presence of a patient having endogenous levels of sulfhydryl donors); page 22, lines 7-10 (teaching that plasminogen or plasmin may be supplied endogenously or administered to the animal); and by Claims 29-30 as originally filed with the patent application (claiming a container holding a plasminogen activator alone or in combination with a sulfhydryl donor with instructions for administering the activator alone or in combination with the donor to treat an animal suffering from an angiogenic disease).

With respect to U.S. Application No. 08/710,305 (now U.S. Patent No. 5,801,012) the Applicant invites the Examiner's attention to page 3, line 33 to page 4, line 13 (describing a method of treating an angiogenic disease by administering a sulfhydryl donor with plasminogen activator and/or plasminogen or plasmin as well as a container with instructions for administering the plasminogen activator with or without a sulfhydryl donor to an animal suffering from an angiogenic disease); page 8, line 33 to page 9, line 18 (disclosing specific plasminogen activators and sulfhydryl donors); page 13, lines 34-35 (disclosing that it is "possible" for any "compound of the present invention to be administered alone," such as plasminogen activator with or without a pharmaceutical formulation); page 14, lines 22-29 (describing therapeutically effective doses of the active ingredient); page 35, line 32 to page 36, line 13 and Figures 7-8 (teaching that an amount of angiostatin may be generated by plasminogen activators administered in the presence of "flow-through" or RPMI containing sulfhydryl donors thereby indicating that the *in vivo* administration of plasminogen activator alone may generate angiostatin in the presence of a patient having endogenous levels of sulfhydryl donors); page 4, lines 2-3 (teaching that plasminogen or plasmin may be supplied endogenously or administered to the animal); and by Claims 17-18 as originally filed with the patent application (claiming a container holding a plasminogen activator alone or in combination with a sulfhydryl donor with instructions for administering the activator alone or in combination with the donor to treat an animal suffering from an angiogenic disease).

## 2. Rejection Under 35 U.S.C. §101, Double Patenting

The Examiner has provisionally rejected Claims 19, 20, and 23 under the judicially created doctrine of obviousness-type double patenting as unpatentable over claims 65-68 of U.S. Application No. 08/991,761. The Applicant respectfully requests that the Examiner hold this rejection in abeyance until the claims are otherwise deemed allowable, at which time the Applicant will consider submitting a terminal disclaimer depending on the claims deemed allowable.

## 3. The Rejection Under 35 U.S.C. §112 Second Paragraph, Should Be Withdrawn

The Examiner has rejected Claims 21 and 24 under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicant regards as the invention because it is not clear what an amount of effective plasmin or plasminogen is effective for.

The Applicants have amended Claims 21 and 24 by deleting the term "effective" thereby mooting the rejection. Accordingly, the rejection under 35 U.S.C. §112, second paragraph should be withdrawn.

## 4. The Rejection Under 35 U.S.C. §112 First Paragraph, Should Be Withdrawn

The Examiner has rejected Claims 19-21 and 23-24 under 35 U.S.C. § 112, first paragraph for lack of enablement/utility because the specification, *while enabling for a method of treating cancer*, does not provide enablement for a method of treating an angiogenic disease by administering a plasminogen activator with or without a sulfhydryl donor. According to the Examiner, one cannot extrapolate the teaching of the specification to the scope of the claims because it is unpredictable that administration of a plasminogen activator alone or in combination with a sulfhydryl donor would be *useful* for treating *any* angiogenic disease.

In response, it is respectfully noted that cancer is an angiogenic disease. The Applicant is not required to have a *separate* disclosure for the treatment of each and every type of angiogenic disease in order to describe and claim a method of treating an angiogenic

disease. The Applicant is only required to show a reasonable correlation between the claimed therapeutic use and the biological activity/result after administration of the claimed compound(s). *See* MPEP § 2107.03 entitled "Special Considerations for Asserted Therapeutic or Pharmacological Utilities" and MPEP § 2107.01, subsection IV entitled "Relationship Between 35 U.S.C. § 112, First Paragraph, And 35 U.S.C. 101." According to MPEP § 2107.03, subsection III:

> If *reasonably correlated* to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or a combination thereof *almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition, or process.* A cursory review of cases involving therapeutic inventions . . . illustrates the fact that *the Federal courts are not particularly receptive to rejections . . . based on inoperability [or unpredictability].* Most striking is the fact that in those cases where an applicant supplied a reasonable evidentiary showing supporting an asserted therapeutic utility, almost uniformly the . . . rejection was reversed (emphasis added).

Here, as noted by the Examiner, the present application discloses that a cancer patient who received a single treatment with urokinase plasminogen activator alone or in combination with a sulfhydryl donor had more than 80% tumor regression as well as a significant increase in plasma angiostatin levels (Table 4, Figures 17A & B). Furthermore, Figures 10-12 demonstrate that plasminogen activators with or without sulfhydryl donors generate angiostatin *in vitro* and Figures 3-5 show that angiostatin generated *in vitro* inhibits cell proliferation (*in vitro*) as well as angiogenesis *in vivo*. Thus, the correlation between the claimed therapeutic use of treating an angiogenic disease by administering a plasminogen activator with or without a sulfhydryl donor and the result (e.g. increase in angiostatin, inhibition of angiogenesis, or tumor regression) is not only reasonable but is clear and unequivocal.

In addition, the Applicant invites the Examiner's attention to MPEP § 2106.01 under the heading "Enablement" which states that "[w]hen basing a rejection on the failure of the applicant's disclosure to meet the enablement provisions . . . the examiner must establish on the record that he or she has a *reasonable basis* for questioning the adequacy of the disclosure . . . " Likewise, according to MPEP § 2107.02 under subsection III, citing *In re Brana*, 51 F3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995), an applicant's assertion of enablement creates a presumption of enablement:

> [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of statements contained therein which must be relied on for enabling support (emphasis added).

Here, the disclosure at page 3, line 12 to page 4, line 7 and page 18, line 26 to page 20, line 10 specifically teaches a method of treating an animal suffering from an angiogenic disease by administering a plasminogen activator alone or in combination with a sulfhydryl donor and/or with plasminogen or plasmin. The specification also teaches the use of specific plasminogen activators and sulfhydryl donors at page 10, lines 1-7, 14-18 and the treatment of several human cancer patients by administering plasminogen activator alone or in combination with a sulfhydryl donor at page 48, line 4 to page 51. In short, the specification teaches the manner and process of making and using the invention in terms which correspond in scope with the pending claims and therefore there is a presumption of enablement. The Examiner has neither presented a reasonable basis for rejecting the claims based on enablement or overcoming the presumption of enablement. Accordingly, the rejection under 35 U.S.C. § 112, first paragraph for lack of enablement/utility should be withdrawn.

withdrawn

**5. <u>The Rejection Under 35 U.S.C. §102(b) Should Be Withdrawn</u>**

Claim 19 is rejected under 35 U.S.C. §102(b) as being anticipated by Meehan et al. ("Meehan") or Calvo FA et al. ("Calvo") "as evidenced by" U.S. Patent No. 4,968,494 ("the '494 patent"). According to the Examiner, Meehan teaches urokinase therapy in small cell carcinoma of the lung and Calvo teaches urokinase combination chemotherapy. The Examiner uses the '494 patent to inherently show that the urokinase used in Meehan and Calvo is a plasminogen activator capable of converting plasminogen to plasmin. According to the Examiner Meehan and Calvo (independently of each other) expressly or inherently describe the same method steps as in Claim 19 using the same composition and therefore the claimed method will inherently lead to the claimed effects.

A claim is anticipated under 35 U.S.C. § 102(b) *only if each and every element* as set forth in the claim is found, either expressly or inherently described, in a single prior art

reference. MPEP 2131; *Herman v. William Brooks Shoe Company*, 2001 WL 312301 at **2 (Fed. Cir. 2001); *Helifix Ltd. v. Blok-Lok, Ltd.*, 208 F.3d 1339, 1346 (Fed. Cir. 2000); *In re Paulsen*, 30 F.3d 1475, 1478-79, 31 USPQ 2d 1671 (Fed. Cir. 1994); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379, 231 USPQ 81, 90 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987). The identical invention must be shown in as complete detail as is contained in the claim. *Id.* Furthermore, the reference must be enabling and describe the applicant's claimed invention sufficiently so that one of ordinary skill in the art could practice the invention. *Helifix Limited*, 208 F.3d at 1346; *In re Paulsen*, 30 F.3d at 1479; *Herman*, 2001 WL 312301 at **2.

Under 35 U.S.C. §102(b), only a *single* prior art reference can be used to show anticipation of a claim. Other secondary references can only be used to show: (1) that the disclosure of the primary reference is enabled (based on what was known in the prior art before the Applicant's invention); (2) to explain (but not expand) the meaning of a term used in the primary reference; or (3) to show that a characteristic not disclosed in the primary reference is inherent ("necessarily" present in the thing described in the primary reference which would be recognized by persons of ordinary skill). MPEP § 2131.01; *In re Donohue*, 766 F.2d 531, 534, 226 USPQ 619 (Fed. Cir. 1985); *In re Baxter Travenal Labs.*, 952 F2d at 390; *Continental Can Co. USA v. Monsanto Co.*, 948 F2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991); *Scripps Clinic & Research Foundation v. Genentech, Inc.* 927 F.2d 1565, 1566-67, 18 USPQ2d 1001 (Fed. Cir. 1991).

**A. Neither Meehan or Calvo Anticipate Claim 19**

Neither Meehan or Calvo anticipate claim 19 because neither reference teaches each and every element of Claim 19, as amended, either expressly or inherently. Accordingly, the rejection based on Meehan or Calvo should be withdrawn.

Claim 19, as amended, more precisely specifies administering "a *therapeutically effective amount* of plasminogen activator *effective to increase the amount of angiostatin present in said animal* to treat the angiogenic disease." Neither Meehan or Calvo teach administering urokinase or any other plasminogen activator in "*a therapeutically effective amount*" which is "*effective to increase the amount of angiostatin*" present in an animal to treat said animal's angiogenic disease. Both references fail to disclose any effect on

the amount of angiostatin present in the patients treated or its effect on angiogenesis. Nor is it inherent that the amount of urokinase used in Meehan or Calvo for treating small cell carcinoma of the lung is "a therapeutically effective amount" which would have "increased" the amount of angiostatin present in the patients to treat their disease.

Meehan itself demonstrates that an increase in angiostatin *in fact did not occur*. According to the present invention, plasminogen activator (administered alone in therapeutically effective amounts) first converts plasminogen to plasmin (assuming sufficient endogenous levels of plasminogen are present). Then a sulfhydryl donor (which may be administered or supplied endogenously by the patient) is required to convert plasmin to angiostatin. During the first step of this biochemical pathway, plasmin levels are expected to increase which can be measured by measuring the level of fibrinogen, D-dimer, and fibrin split products. This is because it is well known in the art that plasmin degrades fibrinogen into D-dimer and fibrin split products (thereby decreasing fibrinogen levels and increasing D-dimer and fibrin split product levels). However, Meehan reports *no changes* in the fibrinogen, D-dimer and fibrin split products in the patients treated. Since no changes occurred in fibrinogen, D-dimer, and fibrin split product levels, additional plasmin was not generated by the patient in Meehan; as a result additional plasmin was not available as substrate for increased angiostatin generation. *See* Meehan at page 108, second column, second paragraph, entitled "Results of analysis of peripheral blood tests," which states:

> *[N]o changes were observed* between pre and post-u-PA infusion blood specimens *for the fibrinogen, D-dimer, and fibrin split product levels*. This is attributed to the fact that the dose of u-PA selected for administration in this study, based on previous work by *Calvo et al*, is known to be lower than is required to induce systemic fibrinolysis (emphasis added).

Thus, because no change occurred in fibrinogen, D-dimer, and fibrin split product levels, no increase in plasmin occurred and therefore the amount of angiostatin could not have increased. The lack of plasmin generation in Meehan is indicative that: (1) the dose of urokinase was insufficient to generate plasmin; and/or (2) the patient lacked a sufficient endogenous supply of plasminogen substrate to be converted to plasmin; and/or (3) the patient lacked or possessed other endogenous factors and/or *in vivo* conditions which prevented the generation of plasmin from occurring. As a consequence, since no plasmin substrate was generated for angiostatin production, an increase in the amount of angiostatin

could not have occurred. Likewise, no angiostatin production could have occurred in Calvo because Calvo uses the protocol described in Meehan. According to Meehan at pages 110-111:

> The dose of u-PA used in this study (*which was identical to that used by Calvo and associates* [*citing* Calvo FA, et al., *Urokinase Combination Chemotherapy in Small Cell Lung Cancer*, CANCER 1992; 70: 2624-2630]) was lower than that considered optimal for induction of intravascular fibrinoylysis. No evidence of systemic fibrinolysis was observed following u-PA infusion in the patient (emphasis added).

Elsewhere Meehan states that "the dose of u-PA selected for administration in this study, based on previous work by Calvo et al. [*citing* Calvo FA, et al., *Urokinase Combination Chemotherapy in Small Cell Lung Cancer*, CANCER 1992; 70: 2624-2630] is known to be lower than is required to induce systemic fibrinolysis." *Id.* at 108. In contrast, the dosing regimen of the presently claimed invention may be adjusted to ensure that the dosage given is therapeutically effective, *i.e.* sufficient to increase angiostatin levels. *See* page 22, lines 13-32 of the specification and page 34, line 6 to page 36, line 5 as well as Example 5 of the specification which describes the use of immunoassays to monitor a patient's serum during treatment.

Accordingly, since neither Meehan or Calvo expressly or inherently disclosed an increase in the amount of angiostatin present in the patients treated, both Meehan and Calvo fail to disclose each and every element of Claim 19. Therefore, under 35 U.S.C. §102(b), Meehan and Calvo do not anticipate Claim 19.

Moreover, even in the absence of the above analysis, where it might be unknown or only a possibility that the dose of urokinase administered in Meehan or Calvo may or may not have increased the amount of angiostatin present in the patients, inherency could not be established.. The Examiner must show that this effect *necessarily* occurred. According to MPEP § 2112, fourth paragraph, entitled "Examiner Must Show Rationale Or Evidence Tending To Show Inherency," the fact that a certain result or characteristic *may* occur or be present in the prior art is not sufficient to establish inherency of that result or characteristic. Inherency "may not be established by *probabilities or possibilities*. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Id.*, *In re Rijckaert*, 9 F.3d 1531, 1534, 28 U.S.P.Q.2d 1955, 1957 (Fed. Cir. 1993) (reversed

rejection because inherency was based on what would result due to optimization of conditions, not what necessarily occurred in the prior art).

Thus, the Examiner bears the burden of proving that the amount of urokinase administered to the patients in Meehan or Calvo under those circumstances and in those patients actually caused an increase in the amount of angiostatin (not the mere possibility or probability that an increase occurred). It should be noted that the burden of proof shifts to the Applicant only after inherency is shown by the Examiner. Here, the Examiner can not meet that burden since Meehan itself shows that an increase in angiostatin could not have occurred in the patients treated in either Meehan or Calvo.

In addition, the Examiner can not claim that the Office does not have the facilities and resources to provide the factual evidence needed in order to establish that the prior art does not possess the inherent characteristic because the Examiner must first show that the characteristic is in fact inherent. *See* MPEP § 2112, fourth paragraph, entitled "Examiner *Must Show* Rationale Or Evidence Tending To Show Inherency," and MPEP § 2112, seventh paragraph, entitled "Once . . . the Examiner Presents Evidence Or Reasoning Tending to Show Inherency, The Burden [Then] Shifts to the Applicant . . . "

Furthermore, to show that a characteristic not disclosed in the primary reference is inherent it must be shown that the characteristic not disclosed is necessarily present in the reference *and would be recognized by persons of ordinary skill.* MPEP § 2131.01, subsection III entitled "To Show That a Characteristic Not Disclosed in the Reference is Inherent." No person of ordinary skill in the art would have recognized that administering urokinase under the conditions set forth in Meehan or Calvo would have increased the amount of angiostatin in patients with small cell carcinoma of the lung.

In view of the foregoing, the rejection under 35 U.S.C. § 102(b) based upon Meehan or Calvo should be withdrawn.

**6. <u>The Rejection Under 35 U.S.C. § 103(a) Should Be Withdrawn</u>**

Claims 19, 20, and 23-24 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Meehan or Calvo in view of Volpert et al. ("Volpert"), Reddy et al. ("Reddy") and the '494 patent. According to the Examiner: (1) Meehan teaches urokinase therapy in small cell carcinoma of the lung, wherein the tumor has decreased in size by about

75%; (2) Calvo teaches urokinase combination therapy; (3) Volpert teaches that captopril inhibits angiogenesis, and could be used for treating arthritis, diabetic retinopathy, atherosclerosis, and cancer, all of which are angiogenesis dependent; (4) Reddy teaches that captopril has antimitotic activity and down regulates growth-related gene expression in pancreatic cancer cells independently of angiogenesis activity; and (5) the '494 patent teaches that plasminogen is converted to plasmin by a plasminogen activator.

The Examiner states that it would have been obvious to treat an angiogenic disease such as cancer by administering a plasminogen activator with or without a sulfhydryl donor because (1) both Meehan and Calvo teach using plasminogen activators to treat lung cancer; (2) Volpert and Reddy teach that captopril (a sulfhydryl donor) can be used to treat a variety of angiogenic diseases, including cancer; (3) a plasminogen activator and a sulfhydryl donor such as captopril could kill tumor cells by different mechanisms, one through acting on plasminogen, and the other through down regulating growth related gene expression; and (4) combination therapies using different drugs is common in the art for enhancing their therapeutic effects. Thus, according to the Examiner, one of ordinary skill in the art would have been motivated to treat an angiogenic disease, such as cancer, by administering a plasminogen activator, a sulfhydryl donor, and plasminogen with a reasonable expectation of success.

Besides the factual inquires recited by the Examiner and set forth in *Graham v. John Deere Co. of Kansas City.*, 383 U. S. 1, 17, 148 USPQ 459, 460 (1966) a determination of obviousness under 35 U.S.C. § 103(a) also requires: (1) that the claimed invention be considered as a whole; (2) the references be considered as a whole and suggest the desirability or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings; (3) that all the claim limitations be taught or suggested; (4) that the references be viewed without the benefit of impermissible hindsight; and (5) that there be a reasonable expectation of success. *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5 (Fed. Cir. 1986); *In re Jones*, 958 F.2d 347, 351 (Fed. Cir. 1992); *In re Vaeck*, 947 F2d 488 (Fed. Cir. 1991); *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988). *In re Royka*, 490 F2d 981 (CCPA 1974); *In re McLaughlin* 443 F2d 1392, 1395 (CCPA 1971). Secondary considerations such as commercial success, long-felt but unsolved needs, failure of others, and unexpected

results, if present, must additionally be considered in determining questions of obviousness. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538-39, 218 USPQ 871, 879 (Fed. Cir. 1983); *In re Merck & Co., Inc.*, 800 F.2d 1091, 1096, 231 USPQ 375, 378 (Fed. Cir. 1986).

Claims 19, 20, and 23-24, as amended herein, are not obvious under 35 U.S.C. § 103(a) because: (1) all the claim limitations are not taught or suggested; (2) the increase in angiostatin after administration of plasminogen activator with or without a sulfhydryl donor is an unexpected result and there was no reasonable expectation of success of such a result prior to the present invention; and (3) there is no motivation to combine the references.

**A. The Claim Limitations Are Not Taught Or Suggested By The Prior Art**

Claims 19, 20, and 23-24, as amended, more precisely require that the plasminogen activator be administered in a "*therapeutically effective amount*" effective to "*increase the amount of angiostatin*" present in the animal to treat the animal's angiogenic disease. Neither Meehan, Calvo, Volpert, Reddy, or the '494 patent disclose, describe, or suggest that the administration of a plasminogen activator (in any amount), or the combination of a plasminogen activator and sulfhydryl donor (in any amount), increases the amount of angiostatin present in a human to treat his/her angiogenic disease. Nor do Meehan, Calvo, Volpert, Reddy, or the '494 patent disclose, describe, or suggest that the dosing regimen may be adjusted (or that an immunoassay may be used to monitor a patients serum) to ensure that the dosage given is a therapeutically effective amount effective to increase angiostatin levels.

This is true whether the references are viewed alone or viewed in combination with each other. Nor are the new limitations inherently disclosed by the references for the reasons stated above. (The rules of inherency under MPEP § 2112 apply to rejections under 35 U.S.C. § 102 as well as to rejections under 35 U.S.C. § 103 for obviousness. *See* MPEP § 2112). Inherency may not be established by *probabilities or possibilities*. The mere fact that a certain thing may result from a given set of circumstances is not sufficient for inherency" (MPEP § 2112, fourth paragraph); *In re Rijckaert*, 9 F.3d 1531, 1534, 28 U.S.P.Q.2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what necessarily occurred in the prior art). Here the

evidence of record shows the opposite. The data reported in Meehan itself shows that an increase in angiostatin did *not* occur in the patients treated in either Meehan or Calvo. As a result of all of the above, all the claim limitations in Claims 19, 20, and 23-24 are not expressly or inherently disclosed by the prior art and therefore such claims are not obvious under 35 U.S.C. § 103.

**B. The Increase in Angiostatin After Administration of Plasminogen Activator With or Without a Sulfhydryl Donor Is an Unexpected Result and There Was No Reasonable Expectation of Success of Such a Result at the Time of the Invention**

As stated above Claims 19, 20, and 23-24 have been amended to require that the plasminogen activator be administered alone or in combination with a sulfhydryl donor in a "*therapeutically effective amount*" effective to "*increase the amount of angiostatin*" present in the animal to treat the animal's angiogenic disease. Meehan, Calvo, Volpert, Reddy, and/or the '494 patent do not teach, disclose, suggest, or indicate in any way that the administration of a plasminogen activator (in any amount), or the combination of a plasminogen activator and sulfhydryl donor (in any amount), would increase the amount of angiostatin present in an animal to treat said animal's angiogenic disease. Thus, the increase in the *in vivo* level of angiostatin claimed in the present invention to treat cancer and other angiogenic diseases is an unexpected result and therefore is evidence of nonobviousness. *See* MPEP § 716.02(a), under the heading entitled, "Presence Of An Unexpected Property Is Evidence of Nonobviousness."

Moreover, there is simply no disclosure, suggestion, or indication in any of the references cited or in the prior art that there would have been *a reasonable expectation of success in obtaining an increase in angiostatin* after administering a plasminogen activator with or without a sulfhydryl donor. One of ordinary skill in the art at the time of the invention could not have reasonably predicted such an increase in the amount of angiostatin present in a human after administering the claimed compounds. Moreover, Meehan casts doubt on the value of urokinase plasminogen activator as an anti-tumor agent, regardless of its mechanism of action. For example, Meehan states at page 110:

> The results of the present study do not define the value of u-PA [urokinase plasminogen activator] treatment of SCCL [small cell carcinoma of the lung]. Although the biopsy was obtained after the lesion had diminished in size by

> approximately 75%, this reduction in tumour size may have resulted in part from the chemotherapy, u-PA, warfarin or a combination of these treatments. The purpose of these studies was not to prove that the u-PA administered had an effect on tumour response. Rather, these studies provide insight into the fate of infused u-PA and, therefore, into possible mechanisms of effect of u-PA infusion in patients with SCCL.

Under 35 U.S.C. § 103(a) if there is no reasonable expectation of success demonstrated by the references a rejection based on obviousness is improper. *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1207-08, 18 USPQ 2d 1016, 1022-23 (Fed. Cir. 1991); *In re Merk & Co., Inc.*, 800 F2d 1091, 231 USPQ 375 (Fed. Cir. 1986); MPEP § 2143.02. Accordingly, Claims 19, 20, and 23-24 are unobvious over Meehan, Calvo, Volpert, Reddy, and the '494 patent taken alone or in combination with each other because the references fail to demonstrate a reasonable expectation of success in obtaining an increase in the amount of angiostatin after administering the claimed compounds. In addition, Claims 19, 20, and 23-24 are also unobvious over Meehan, Calvo, Volpert, Reddy, and the '494 patent taken alone or in combination with each other because the increase in angiostatin after administration of a plasminogen activator with or without a sulfhydryl donor is an unexpected result.

**C. There Is No Motivation to Combine the References**

In rejecting claims under 35 U.S.C. § 103(a) for obviousness there must be some motivation or suggestion, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. MPEP § 2143. "The mere fact that references *can* be combined or modified does not render the resultant combination obvious unless the prior art suggests the desirability of the combination." *See* MPEP § 2143.01, under the heading entitled, "Fact That References Can Be Combined Or Modified Is Not Sufficient To Establish *Prima Facie* Obviousness." In the present Office Action the Examiner does not disclose what, how, why, or where the motivation is to combine Meehan or Calvo with Volpert, Reddy, and/or the '494 patent. The Examiner simply states that one of ordinary skill in the art "*would have been motivated*" to treat an angiogenic disease, such as cancer, comprising administering a

plasminogen activator, a sulfhydryl donor, and plasminogen with a reasonable expectation of success."

However, under MPEP § 2143.01, a statement that modifications of the prior art to meet the claimed invention "would have been well within the ordinary skill of the art at the time the claimed invention was made because the references relied upon teach that all aspects of the claimed invention were individually known in the art" is not sufficient to establish a prima facie case of obviousness without some *objective reason* to combine the references. *See* MPEP § 2143.01, under heading entitled, "Fact That The Claimed Invention Is Within The Capabilities Of One Of Ordinary Skill In The Art Is Not Sufficient By Itself To Establish *Prima Facie* Obviousness." Here, the Examiner has provided no objective reason to combine the references. The only reason provided by the Examiner to combine the references is the mere fact that references can be combined and that one or ordinary skill in the art would have expected the combination therapy to be useful because combination therapies using different drugs is common in the art for enhancing their therapeutic effects.

However, the burden remains with the Examiner to provide an objective reason to combine the references. *See* MPEP § 2142, third paragraph, under the heading entitled, "Establishing A *Prima Facie* Case of Obviousness" (When the motivation to combine the teachings of the references is not immediately apparent, "*it is the duty of the Examiner to explain why the combination of the teachings is proper*." Accordingly, since the Examiner has not provided an objective reason to combine the reference teachings of Meehan or Calvo with Volpert, Reddy, and/or the '494 patent, a rejection under 35 U.S.C. § 103(a) can not be properly sustained with respect to Claims 19, 20, and 23-24 (as amended).

## CONCLUSION

Entry of the foregoing remarks and amendments is respectfully requested. Applicants believe the claims to be in condition for allowance. An early allowance is earnestly sought. No fee is believed to be due with this Amendment other than the fee for the Petition For Extension of Time. However, if any other fee is required, please charge the fee to Pennie & Edmonds LLP Deposit Account No. 16-1150. If any issues remain, the Examiner is requested to telephone the undersigned at (212) 790-9090.

Respectfully submitted,

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Date: July 1, 2002

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Enclosures